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May 24, 1990

Organized by the

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EXECUTIVE SUMMARY

The Department of National Health and Welfare organized this workshop with two main purposes: a) to identify and develop priorities for multidisciplinary research into the condition and b) to identify educational/health promotion needs and explore social problems of affected persons. The workshop was chaired by Dr. Irvin Broder from the Gage Research Institute, Toronto.

Workshop participants included medical experts, health researchers and representatives of the Allergy Information Association, The Allergy and Environmental Health Association, the Canadian Society for Environmental Medicine, The Canadian Society of Allergy and Clinical Immunology (CSACI), the Canadian Public Health Association and the Canadian Medical Association.

The morning session consisted of talks on seven selected topics followed by questions and discussion.

There appeared to be general agreement that there are many persons who are unusually sensitive to chemical and other substances in the environment and that some may be quite ill. Clinical experience indicates there appears to be a growing number of these persons. Psychosocial debility may be quite prominent. The lack of readily available routine diagnostic tests and the controversial nature of some tests in use make diagnosis difficult. The medical label given to a patient may lead to problems qualifying for various disability benefits. Given its clinical prominence and the attendant socioeconomic costs, multiple chemical sensitivities (MCS) is worthy of serious scientific study. In the meantime, however the patient should not be caught in the medical debate -and denied social benefits. Benefits should be based on defined functional disabilities, not on the medical label. Ministries of Health should be responsible for ensuring that there is no discrimination against patients by insurance companies in regard to coverage for medical related expenses.

Following this session the delegates broke into four working groups. Each working group discussion was summarized by a rapporteur at the closing plenary which led to further exchanges.

Because of the diversity of symptoms and limited physical or laboratory abnormalities, establishing a working definition for research purposes proved difficult. The epidemiology working group reported that research on environmental sensitivity should begin at a very basic level. Several approaches are possible: a) case series reports as a starting point, b) population surveys based on questionnaires and c) case control studies with clinical and lab evaluation and environmental assessment. It was felt that inhalation or oral challenges should be carried out in a few specialized centres. A controlled human environmental research facility requires the dedicated efforts of a large team of specialists.

The following recommendations were made by each of the working groups. Recommendations were broad in scope and were directed at Provincial ministries of health, voluntary agencies, scientific bodies, medical schools, individual researchers as well as the Department of National Health and Welfare.

SUMMARY OF RECOMMENDATIONS

A. EPIDEMIOLOGY

1. A recommended definition for environmental sensitivity is "idiopathic, poly-system, symptom complex," with the symptoms having a definite time frame and being associated with particular environmental stimuli.

2. A series of case reports would be a useful starting point.

3. General population surveys are needed to determine the prevalence of the condition, either from scratch or by the use of some current data bases, such as, for example, the Ontario Health Survey or Enquête Santé Québec.

4. Options to define either a syndrome or a disease from survey data could be either, *a priori* definitions based on expert advice, or some form of statistical analysis of the data such as cluster analysis, principal components analysis, correspondence analysis, etc.

5. There is a need for analytical studies to identify risk factors. A further meeting would be necessary to discuss how to proceed with such studies. Perhaps it would be useful to group those being studied into different populations, based for example on age, occupation, geographic locale, etc. It might be possible to define groups of symptoms that appear to occur more often in combination than one would predict.

6. In a large random survey, the few having serious symptoms can be missed. A method must be developed to pick up these people.

B. CHALLENGE STUDIES

7. With ingestional challenge, symptoms, whatever they are, need to be reproducible in a consistent manner with specific foods or food additives that the patients thought they were sensitive to. They need to be double blind placebo controlled.

8. A modified restricted elimination diet should be used for one to two weeks; however, because of problems with nutritional deficiencies the maximum should be four weeks. If patients improve on the diet, they should be challenged with the food or food additive found to be most offensive. A maximum of one challenge per week is thought to be the optimum. Patients should be watched for four hours after the challenge.

9. Challenge should be done over two hours with food being given at fifteen-minute intervals. The total dose that should be given is 10-15 grams with a maximum of 100 grams. The amount varies depending on the individual food under scrutiny. If a consistent response was not achieved, the challenge should be repeated. The need for an objective end point is emphasized. Odour and taste affect somatic responses. Disguising taste and smell may obliterate important stimuli.

10. Inhalation challenges should be carried out in a few specialized centres.

11. An adequate history, in terms of exposure and symptoms, is required and a standardized assessment and questionnaire should be used.

12. In determining objective end points, wheezing with changes in pulmonary function, and changes in nasal flow rates should be used.

13. With those having subjective symptoms, it would be necessary to do careful placebo control challenges. This should be done using a standardized and detailed assessment with the chemicals under scrutiny concealed. An attempt to carefully score the symptoms should be made to provide some degree of quantitative assessment. There has to be reproducibility of the technique and a uniformity in the quality control. The studies should be double blind placebo controlled.

14. The chemicals used in challenge could be a single substance or crude mixture (i.e., gasoline fumes). If abnormalities are found then an analysis of the mixture to identify its components should be undertaken.

C. LABORATORY APPROACHES

15. An epidemiological definition of the syndrome with clinical and basic science input is required.

16. Scientific conclusions need to be based on collection of data from individuals affected and their environments (home, office etc).

    Evaluation of the patient includes a questionnaire, clinical and laboratory tests, with specific attention focused on areas of sensitivity such as the eyes, nasal passages, salivary glands, autonomic nervous system, etc. which should precede neuropsychiatric workup.

17. For sampling in the home or work environment, tests may include assessment of various allergens (moulds, house dust, mites) as well as airflow, air quality, humidity and temperature.

18. Basic laboratory studies on toxicology and nutritional abnormalities should be undertaken.

19. Future directions should include a patient registry, data bank and specimen banking system.

D. SOCIAL AND EDUCATIONAL NEEDS

20. Minimum educational requirements should be established for those using the term clinical ecologist. "Environmental physician" would better denote an M.D. with interest and training in environmental medicine.

21. A central registry of physicians should be developed who have appropriate training in this field, and who are sympathetic to the plight of those with environmental sensitivities.

22. These proceedings, and the results of the Ontario Ministry of Health Studies on Food Allergy should be published in widely-read medical journals to raise professional awareness.

23. Health and Welfare Canada and/or the CPHA should sponsor a national conference on environmental sensitivities, and devise a format for more local awareness-raising seminars.

24. Provincial ministries of health, provincial hospital associations, and provincial medical associations should sponsor provincial conferences, and include university educators.

25. Knowledge of environmental sensitivities should be imparted to medical students, and to practising physicians through CME programs.

26. The Allergy Information Association, and the Allergy and Environmental Health Association should co-sponsor workshops to draw together the different players who are essential from the environmentally sensitive consumer's point of view.

27. Other groups of doctors besides allergists should receive patient information and newsletters from the Allergy Information Association.

28. GPs should be the frontline workers, referring appropriately to specialists, and then co-ordinating treatment plans.

29. A few specialized teams should be developed across the country to act as resources to deal with environmental illness particularly in its severe form.

30. The public, patients' organizations, physicians, and MPs should continue to exhort all levels of government, as this will encourage the development of further government health policies regarding environmental sensitivities, and acceptable public education literature, and, ultimately, a health promotion campaign.

31. Focus should be maintained on the "wellness" or "green" model of the health of the whole patient and the whole environment.

32. Environmentally sensitive patients should not be dismissed as "neurotic", but receive respect and support.

33. Physicians who show interest in the field should not be stigmatized, and should be adequately compensated for the time they spend with patients with complicated illnesses.

34. Health and Welfare Canada should consult with provincial ministries of health to ensure appropriate medical care is provided to environmentally sensitive patients.

35. Education and policy initiatives initially should take place in areas where there is the most sympathy regarding environmental sensitivities, and the most willingness to change.

36. Ways should be found to help patients while epidemiological research proceeds.

37. A pilot study should be done in a selected community, of the prevalence of environmental sensitivities, the needs of patients, and models for treatment. Application for grant money to get the various agencies and interest groups together for such a project should be made to N.H.R.D.P. or other agencies with available funds.

38. Disabilities should be rated functionally rather than diagnostically in considering eligibility for pensions/social assistance.

39. Provincial ministries of health, which licence insurance companies, should ensure there is no discrimination against environmentally sensitive patients with regard to payment for medications, assistive devices, and other illness-related expenses.

PREFACE

In recent years increasing attention has been directed to the assessment of the impact of environmental exposures on human health. Growing concern has been expressed about possible adverse health effects of many substances even at low levels of exposure.

While there is growing evidence to support the view that a significant number of persons are unusually sensitive to chemical substances in the environment in addition to the traditional allergies, information on its prevalence is virtually non-existent. A reluctance to accept the syndrome by some may stem from the lack of known and-or obvious mechanisms. There is a need for facts, clear cut definitions and diagnostic criteria as well as basic scientific and epidemiological research to try to clarify the nature of the problem.

A meeting was held late in 1989 by a number of professional and lay associations dedicated to helping patients with allergic illnesses and environmental sensitivities. As a result there was agreement on the following points:

- There is a large burden of illness.

- There is much to be learned about the conditions.

- There is a need for multidisciplinary research, and lay and professional education.

- A workshop should be held which would focus on these points.

As a result this workshop was organized by the Bureau of Chronic Disease Epidemiology, Laboratory Centre for Disease Control, with the assistance of professional and lay associations dealing with allergies and chemical sensitivities.

The workshop was held on May 24, 1990 in Ottawa, Ontario, Canada. During the plenary workshop, seven presentations by various experts working in relevant areas were made. The delegates then broke up into four working groups. Each working group discussion was summarized by a rapporteur at the closing plenary, which led to further exchanges.

The workshop was chaired by Dr. Irvin Broder from the Gage Research, Toronto. The following proceedings describing this workshop have been prepared by Jack Basuk, an Ottawa based consultant with the various items presented in chronological order.

WELCOMING AND INTRODUCTORY REMARKS

MINISTERIAL WELCOME:

On behalf of the Minister of Health & Welfare, Perrin Beatty, the workshop delegates were welcomed by Dr. Bruce Halliday, M.P. who then went on to read from a text prepared by the Minister. "I would like to thank you all for taking time from your busy schedules to assist with this workshop. This is an important issue for my Department both from the number of requests I receive from Members of Parliament on behalf of their constituents and the number of letters and calls that Health and Welfare Canada receives on the topic. It obviously reflects, to some extent, at least, the number of persons affected and concerned.

"I understand that very little in the way of formal research has been carried out into this perplexing condition, that there are many theories about its cause, yet little in the way of hard information about its frequency in the community. What is needed now is a concerted effort to find out what is wrong with these persons and the factors that govern their condition. We must arrange free exploration and rational discussion of the problem. Since the main, but not exclusive focus of this workshop is research, my Department has invited researchers from a number of disciplines to discuss the problem and to recommend what research is required. Representatives from the Medical Research Council and the National Health Research and Development Program are here to advise.

"I would particularly extend a welcome and my thanks to our American colleagues for your willingness to participate. I thank you all for taking the time from your busy schedules to help my Department. I hope that as a result of this workshop, we can stimulate the required research into this condition and that possible solutions will emerge.

"I understand that the results of this workshop are to be published. I am encouraged by your willingness to assist and I hope that by bringing you together in this way we can start to address the concerns of those who are affected and help them better understand and cope with the nature of their problems."

CHAIRMAN'S INTRODUCTORY REMARKS:

Dr. Broder opened the workshop with the following statement: "I would like to take this opportunity to deal with a few questions, such as: Why are we here? Why is it necessary to hold an exploratory type of workshop on the problem of environmental sensitivity? and; What do we hope to accomplish today? We are here to discuss environmental sensitivity, mainly as a research problem. We also wish to keep before us the serious social, financial and other difficulties that this problem raises in people who suffer from it.

"I think you are all aware that certain groups feel that there are subsets of environmental sensitivity and possibly this will come up during the various discussions. It is my feeling that we should not try to break up the problem unnecessarily. I would prefer if we direct the discussion on a more general basis without complicating matters by dealing with the individual subsets (unless it is absolutely necessary) that may or may not exist. Environmental sensitivity has been around for, at least, three decades, yet very little is known about it. Despite this, the social disruption that it causes is devastating. It is important that groups such as ours focus on this difficulty with a view to finding some rational basis for investigating it and helping to solve the problem in the future.

"The symptoms of environmental sensitivity are typically diffuse and non-specific. The results of physical examinations and all laboratory investigations are usually within the normal range. The mechanism is totally unknown. The diagnosis tends to be one of elimination and is difficult to substantiate. Treatment is empirical and largely unproven.

"It is obvious that we know about as little about this condition as it is possible to know. It is evident that much work needs to be done.

"As far as what we can hope to accomplish today, I do not think we can be overly ambitious. Through our various working groups, we should try to arrive at a consensus on a reasonable definition for environmental sensitivity. This might be done by adopting an existing published definition, by modifying one of the previously proposed definitions or coming up with something that is more unique and original.

"We will try to foster the research interests of those present who are in a position to conduct independent research and submit grant applications. We should try to establish some research priorities that will help to direct these interests in the most constructive direction."

PRESENTATIONS

1. AN OVERVIEW by DAVID McCOURTIE, MD, FRCP

(What follows is an edited version of a written submission of Dr. McCourtie's presentation)

I would like to thank Dr. Broder and the organizers of this meeting for the invitation to give a brief overview statement. I plan to review some of the important points which I think that we should cover during the day and then leave time for discussion. Each of us has a different viewpoint regarding environmental sensitivity depending upon our background. I come into this area with the background of a fairly traditional allergist. In 1985, I had the privilege of serving on the Thomson Committee and it is of interest that two other members of the Committee, Dr. John Gerrard and Dr. Jim Day are attending this Meeting. I have maintained a continuing interest in environmental sensitivity. Some of the important points in 1985 and which seem to be valid now include our impression that the patients were definitely sick. We were impressed there was some type of illness affecting these individuals. As a practising allergist, I thought that some of them could have been diagnosed in a traditional manner, but there certainly were others where the environmental factor seemed to be very important and the diagnosis, was not readily apparent. We were also impressed about the importance of the medical label that the affected person was given. A traditional diagnosis meant that the individual had a fairly clear easy path in the medical world, while a controversial diagnosis could lead to many difficulties. The social benefits were a third issue and these inter-related with the diagnosis.

It was very difficult for social agencies to deal with a controversial diagnosis and this led to the patient's problem of qualifying for various disability benefits. One of the recommendations of our Committee was to redefine and to increase the social assistance available to individuals who were suffering from environmental sensitivity. We thought they should not be caught in the medical debate about the problem.

There were some controversial points which we spent many hours discussing. The controversial testing procedures used by a number of clinical ecologists were felt to be unproven and not adequate for proper diagnosis in many situations. The testing procedures become very important because they lead to the label or diagnosis applied to the individual which then determines some of the issues that I have mentioned previously. I think that one of our tasks today will be to examine the diagnostic methods available and clearly define acceptable scientific criteria for diagnosis.

Regarding the agenda for today's conference, I think that we are all concerned with people suffering from adverse effects from the environment. Each report or conference which has been held on this subject in the past has made a plea for further research. I would just like to mention a few points which I think have to be stressed.

One of the most difficult areas is a working definition of the illness. Because of the diversity of symptoms the patients suffer and the limited physical or laboratory abnormalities which we can find, the definition has been a continuing problem. It is possible to list a few exclusions. The patient does not qualify if he is reacting to a known toxin or a known allergen or a defined physical factor. Each of those can be measured including the physical triggers such as inadequate ventilation, or inappropriate humidity. Some of the questions which are related to the definition are inclusion of adverse affects from either individual or multiple agents. One has to define the level of exposure necessary for an effect and perhaps include modifying factors which could change the individual's susceptibility. It is quite probable that there are a number of mechanisms whereby the environmental factors cause an adverse effect. The individual's susceptibility is a major question and again it is probably multifactorial. I think that the definition, therefore, will have to be descriptive and we will have to accept a number of limitations. The importance of a definition is obvious as it leads to the next step of setting up the research projects which we will be discussing through the day. Once a definition is generally accepted, we can begin gathering information regarding the incidence, prevalence and the natural history of the illness. Appropriate epidemiologic studies have been supported by several previous reports. We have a number of experts in this area present today who will be discussing this issue.

Challenges to the affected individuals are generally accepted as necessary for diagnosis and for research into areas such as the pathophysiology of the reactions. The challenges can be very simple or very complex and difficult. It is often suggested that a special designed unit would be the best location for such challenges. The hospital unit in Dallas which is run by Dr. Bill Rea is cited as an appropriate example. Several members of the Thomson Committee visited Dr. Reas's unit in Dallas and Dr. Theron Randolph's unit in Chicago back in 1985. One of the problems identified was the commitment of the investigators in these units to one diagnosis. As an example, Dr. Rea and his associates presented information regarding 2,000 patients they had seen in their unit and studied quite

intensively. They had only four negatives. All four individuals where found to have malignancy as part of their investigations. The remaining patients were all diagnosed as environmentally sensitive. There were no appropriate controls and the patient was assumed to have environmental hypersensitivity mainly by being referred to the unit. I think that any unit which is being set up in the future will have to meet much higher scientific standards. These will include careful measurement and biologic purity of the challenge material. There will have to be appropriate placebos and a scientifically accepted endpoint. A clear objective or biochemical endpoint would be most desirable. I think that it is mandatory that whenever possible, the challenge is done in a double blind placebo controlled fashion. Speaking from the allergist's perspective, I think that there is still a great deal of research to be done to be sure that there are no hidden allergic triggers in certain environmental situations. We now know that people transport cat dander from one location to another and this will have to be one of the triggers that are ruled out in any future investigation. The other major question relates to unusual mould antigens which are very difficult to identify and study.

There is also work to be done related to the other issue involving our environment and illness. The social and educational aspect of the problem is intensified by the overwhelming media coverage of any environmental issue. In London, Ontario, there is almost a standard format for every newspaper and television report on this issue. There is usually a sensationalist statement indicating that we are close to the edge of disaster either at a local park or beach or industrial setting. There is a self-proclaimed expert, a university professor who is given at least a quarter page coverage indicating that the authorities are not dealing with the problem properly and that children and pregnant women are certainly destined to have cancer or some other horrible affliction because of their exposure. After two or three years of very expensive study, it is found that the problem really isn't quite that bad and some reasonable action is taken. I think that this process is very dangerous. It breeds fear and anxiety in the general population, who are told the air we breathe, the water we drink and the food we eat are filled with toxic materials. It also produces a completely negative attitude toward the agency which is responsible for maintaining safe levels of various materials in our environment. The assumption is usually put forward that if a chemical or a biological material is present in the environment, it must be harmful. I think that there is very limited scientific value in this kind of statement and certainly in the toxicology literature, there are statements which support exactly the opposite proposition, that is, that many of these materials in low concentrations are actually beneficial. I think that this process makes the results of our conference today very important. I would like to suggest that we should be extremely careful and avoid any inappropriate statements or unfound generalizations. We should carefully avoid sensationalism and try to seek scientific truth so that we can advance the knowledge and understanding available regarding environmental sensitivity.

Thank You

During a brief discussion period following the preceding presentation, the prevalence of environmental sensitivity was questioned. It was argued that there was no basis for the 15% figure proposed by the National Academy of Sciences and that in fact the actual incidence of the Environmental Sensitivity Syndrome is much lower.

In response, one M.D. present stated that nearly all his patients complain of multi symptoms and 70% of them claim to be sensitive to at least one environmental factor. The percentage drops for those claiming two or more such factors. Whether their observations are accurate is difficult to ascertain, particularly since the end point of such sensitivity has, as yet, not been defined. He agreed that it would not be appropriate to extrapolate from his practice to the general population.

2. FOOD CHALLENGE TESTING IN PATIENTS WITH MULTIPLE FOOD-RELATED SYMPTOMS
by SUSAN M. TARLO, MB, FRCPC

(What follows is an edited version of a written submission of Dr. Tarlo's presentation)

To date there is no clearly defined protocol for such challenge procedures, in contrast to the many well defined and good protocols which have been reported for food challenging of patients suspected to have IgE mediated food allergy.

There are several differences in the type of reported responses to foods in patients with multiple food related symptoms (MFRS) not typical of IgE mediated responses. In such patients the reported response is often several hours or even days after ingestion of food as opposed to the rapid onset in IgE mediated responses. Responses are often reported to many different foods in patients with MFRS as opposed to the relatively small numbers of foods in IgE mediated responses. The changes observed are mostly subjective in MFRS as opposed to more objective changes in IgE mediated responses. They have not been documented to be life-threatening in MFRS patients. The MFRS patient may need concurrent foods or concurrent environmental factors to provoke changes while in IgE mediated responses the single food alone will trigger a response. The

reproducibility of responses in MFRS is unknown whereas in IgE responses, over a short period of time, the response may be lost.

Therefore, in MFRS the factors which determine the methods of food challenge will depend in large part on the history given by the patient of the appropriate foods, symptoms produced, time of onset of symptoms, duration of symptoms and severity of symptoms. Other factors which may determine the method of food challenge include the available facilities; for example, the availability of an environmental unit and varying assessment facilities such as a neuropsychopathic assessment.

There are a number of decisions which have to be taken with this type of food challenging. Firstly, one must decide whether to perform the tests as an in-patient or an out-patient; in a normal as compared to a protected environment; which baseline diet should be used and for how long; which food or foods should be used for the challenge; which component or components of these foods may be relevant to the patient's symptoms; what should be the starting dose and the maximal dose given for a good and safe challenge; how can the food be concealed for single or double blind challenge testing; how to assess the response depending on whether it is producing subjective or objective changes; how long to follow the patient in terms of hours, days or weeks and how often should repeat challenges be performed; and finally how to interpret inconsistent responses if challenges are positive on one occasion and negative on another.

Obtaining a baseline prior to challenge testing can pose a problem which needs to be overcome. Medications which may mask the response should be withdrawn except for those which are clearly needed for medical stability. Secondly, the baseline diet should be controlled and this may involve going to the extent of fasting the patient and providing chemical free or distilled water, but in this event, one should recognize that there are risks of causing neuropsychopathic changes even without the challenge intervention. Thirdly, there is a question whether the patient should be completely withdrawn from the environment and placed into an Environmental Care Unit. This is a very expensive and complicated approach and requires the development of very specialized units. There are possible dietary sources of adverse responses to food that should be considered when one is selecting foods for challenge testing. Symptoms may be caused by the actual food itself or by various additives and contaminants such as dyes, flavorings, preservatives, toxins, infectious organisms or accidental contaminants such as heavy metals, pesticides, antibiotics, etc. Methods of blinding the challenges include using opaque gelatin capsules with dextrose or xylose as a filler and placebo and freeze dried foods, frozen if needed, to disguise their taste. Other means include hiding the challenge food or additive in Vivonex, which is flavoured and iced, flavoured milk shakes or ice cream, apple sauce, hamburger, etc., in other words nearly any foods which will mask the texture and taste of the challenge food.

There are problems that can occur with the use of food capsules. One is the volume limitation of foods which can be given in capsules, generally around 8 gms of dried food. Patients with MFRS might require larger volumes to induce symptoms. The food in capsules bypasses the upper GI tract and therefore one may miss responses occurring in this region as might possibly happen with sulphites. The food given in capsules is generally dried and uncooked which may not be the appropriate format for it and the food may be too pure, in other words, it is often given in this form without the additives which are found in real life.

Problems with non encapsulated food include possible difficulty in blinding the challenge or concealing the food adequately and possible difficulty in finding a placebo food which is tolerated by the patient in which to hide the challenge material.

Therefore, when performing food challenges for patients with MFRS, one must first find a placebo that is tolerated in an open manner. It is best to challenge with the food that the patient thinks produces the most definite changes and to increase the challenge amount of this food up to maximal dietary levels, starting with the pure food. If this is negative then adding additives, or other foods, or other environmental factors, in a controlled manner, double or single blind, should be considered. During the challenge testing, multiple placebo days should be used, especially if the response being assessed is predominantly subjective. It has been advised by some authors that at least four days should be allowed between repeat food challenges to avoid masking the effects of initial food administration analogous to the refractory period after ASA. Finally, in patients who have a positive subjective challenge response, the challenge should be repeated on several occasions to assess consistency of response.

Some of the preceding can be illustrated by the findings of a recent study which was performed by Dr. Sharon Parker of the Department of Nutrition at the University of Toronto and in which Drs. Sussman, Leznoff and myself collaborated. The objectives of this study were to compare the clinical, dietary and psychological profiles of adults with either confirmed or unconfirmed reactions to foods. Subjects selected were adults aged eighteen to sixty years with no interfering medical conditions. They were clinically assessed with history, physical examinations and skin prick testing. Double blind food challenges were performed in patients who did not have a history to suggest a life-threatening response. The patients were divided into those who either had a clear history of IgE mediated

symptoms with positive skin test response to the appropriate food or a positive double-blind challenge to that food and those who had symptoms not clearly suggestive of an IgE mediated response and in whom double blind food challenging on an out-patient basis with capsules was negative.

Challenges were performed using freeze-dried foods in gelatin capsules with xylose as a placebo. The response was measured objectively when possible, otherwise, it was assessed subjectively and any positive or questionable response was repeated on at least one further occasion. All the patients in the unconfirmed group had negative challenges as a requirement of their classification. Patients in the so called confirmed group included three patients with positive food challenges. These consisted of a patient with abdominal pain and nausea to clams who was positive on skin test and challenge; a patient with urticaria and itching of the eyes to green beans who was positive to skin test and challenge; and one patient with migraine related to soy who was negative to skin tests but positive on challenge. An additional 19 patients were included in the so-called confirmed group on the basis of a strongly positive history of typical severe allergic symptoms related to a specific food and a positive skin test to that food. They were not challenged due to the severity of their previous response from the history. We then looked further at the characteristics of these two groups of patients to assess the differences.

We ended with 22 patients in the so-called confirmed group, 21 of whom had IgE mediated responses and 23 patients in the so-called unconfirmed group, all of whom had negative double blind challenges. The profile of these two groups of patients showed that those in the unconfirmed group were slightly older and there was a trend to more females and unmarried people in this group.

The symptoms were significantly different between the two groups of patients with swelling, respiratory symptoms and itching being more common in patients with IgE mediated responses and non-specific symptoms being far more common in those who had unconfirmed responses.

Non-specific symptoms reported included dizziness, weakness, migraine headaches, numbness, loss of concentration, confusion, difficulty sleeping, depression, bloating, abdominal distension and gas. Of these, migraine headaches, abdominal distension and various miscellaneous symptoms were more common in the unconfirmed group.

The miscellaneous symptoms included muscle cramps, aches, sweating, chills, pins and needles, hyperirritability, mood swings, hearing impairment, memory loss, sluggishness, constipation, pain in the chest, swollen gums, fatigue, vasculitis, burning mouth, itchy earlobes and swelling within.

The age of onset in the unconfirmed group was older than in those with IgE mediated responses and the time of onset of symptoms was later, occurring, more often, two hours or later after ingestion of food. The duration of symptoms was also longer in this group, being over 24 hours in 56% of the patients and these responses occurred more frequently, daily to weekly in 54% of the patients.

There was a difference in food use between the groups of patients. The unconfirmed group ate more brown rice, Boston bluefish, herbal tea, calcium supplements, lecithin and various other supplements. The patients in the unconfirmed group more often attributed their symptoms to dairy products, meat and grains than those in the confirmed group. Similarly, they were more likely to attribute symptoms to chocolate, white sugar, brown sugar, honey, fried foods, yeast and food additives; liquids such as cola, red wine, carbonated beverages, coffee, beer; fruits and vegetables such as apples, mushrooms, grapefruit, dried fruit, grapes, bananas and cauliflower. These latter differences were all statistically significant.

A psychological assessment was made in those patients and showed that subjects in the unconfirmed group showed significantly higher scores for measures of hysteria, hypochondriasis, somatization and a positive symptom distress index.

In conclusion, subjects with unconfirmed non IgE mediated responses are more likely to exhibit multiple offending foods, non specific symptoms, delayed onset of symptoms, alternative eating patterns and psychological dysfunction.

From this study we were not able to exclude the possibility that patients in the unconfirmed group may have had symptoms triggered by larger amounts of the foods than those we were able to give them in capsules. It is possible that by challenging them in an out-patient setting while avoiding only the suspected foods, they may have had a masking of their symptoms. It is possible that we challenged them with foods that were too pure or did not contain relevant additives. The finding of psychological differences in our two groups does not necessarily imply that these were the cause of their symptoms and we certainly did not exclude the possibility that foods or the environment may have triggered these changes. In order to explore these possibilities, further testing in an Environmental Unit likely would be necessary.

Thank You.

Following the preceding presentation there was a brief exchange about the use of capsules. The view that they have never worked with adults mainly because the amount of suspected food in the capsules is too little was strongly voiced. Work by Atkins was cited. When he obtained double blind negative results from a capsule challenge he resorted to open challenges which usually resulted in positive results. (Dr. Parker, it was felt, was remiss in not following the same procedure.) While this does not prove anything it does suggest that ways to get large amounts in blind studies need to be found. In reply, it was pointed out that Parker et al. had been dealing with an IgE sensitive group and then had defined another group that had not reacted in the same way. It is possible that if the second group were challenged in a different way they may represent an entirely different subset.

3. ROLE OF ENVIRONMENTAL CHAMBERS IN TESTING by JIM DAY, MD, FRCPC

(What follows is a rather brief summary of Dr. Day's presentation. This is because Dr. Day's talk was descriptive, mostly addressing pictorial slides.)

Work with environmental chambers started when the urea formaldehyde controversy erupted. It was necessary to determine whether the problem was due to the release of formaldehyde, dust, particulates, moulds or off gases.

The first approach was to test whether formaldehyde by itself was the culprit. To do this, 0.7 ppm of formaldehyde was introduced into an environmental chamber. It was, presumably, at this level that symptoms were first reported. Patients were exposed for three hours. The humidity and temperature were regulated. No end point results were recognized. Off gases were then added with similar results. Patients were then exposed to urea formaldehyde particulates. Only one patient reacted but he reacted to air alone. This suggests the importance of testing with placebos.

This work with urea formaldehyde led to the concept of an Environmental Chamber which is that of a Controlled Human Environmental Research Facility (CHERF). Some of the technical and commercial applications include:

- the assessment and management of environmentally related illnesses.
- the evaluation of programs already in place.
- the development of more effective gas and ventilation systems.
- improvements in the design of clean air systems.
- development of medical and technical techniques and instruments for detecting the effect of trace materials over short exposure periods.
- the formulation of surface treatment products to reduce the release of air borne toxins from furnishings and interiors.
- the design and development of new types of indoor air cleaners.
- improvements in methods of industrial air sampling and ventilation.

The site of such a facility is important. Ideally it should be near a hospital and in a locale with good ambient air quality. The initial size of the facility should be able to accommodate individual testing, group testing up to 10 subjects for periods longer than 24 hours and larger groups for shorter periods. The whole area should be amenable to temperature, humidity and clean air regulation, while 50% of it should be constructed so that the air pressure within it can be controlled.

Other uses of such a facility can include the assessment of antigen (pollen) exposure as well as evaluating the response to medication under controlled conditions.

Finally, it is obvious that a Controlled Human Environmental Research Facility requires the dedicated efforts of a large team of expert specialists.

Thank You.

4. EMOTION, IMMUNITY and DISEASE by REGINALD GORCZYNSKI, MD, PHD

There are a number of studies which indicate that immune responses are susceptible to regulation by classical conditioning techniques, as originally outlined by Pavlov.

In a taste aversion paradigm a novel taste substance (saccharin, Sacc) is included in an animal's drinking supply on each of several occasions that the animal receives treatment with a known immunosuppressive drug (cyclophosphamide, Cy).

After a number of trials it has been observed that these animals now show a decreased immune response on challenge with, for instance, sheep erythrocytes (SRBC), if this antigen is administered along with Sacc. Results from a typical study are shown in Table 1. In addition to measuring the antibody responses in these mice a behavioural parameter reflecting past exposure to Cy was assessed (taste aversion-see footnotes to Table 1).

Note that on the test trial of all mice re-exposed to Sacc animals were given Sacc-flavoured water at two, four and six days post SRBC. All mice previously treated with Cy gave diminished antibody-forming-cell (AFC) responses relative to non-treated mice (rows 3, 4, 7 and 8). However, only that group in which prior exposure was in the context of Sacc (rows 7, 8) showed enhanced suppression when given Sacc to drink after SRBC (5870 AFC/spleen vs 15960 AFC/spleen in conditioned mice re-exposed to water; p, Wilcoxon Rank Sum Test). These effects are not explainable in terms of Sacc exposure alone; nor apparently, are they associated with non-specific stress/nausea attributable to Cy injection.

The conditioned group re-exposed to Sacc also shows pronounced taste aversion. However, it has been common experience that the taste aversion does not parallel the conditioned immunosuppression in these mice.

Indeed animals in group 8 clearly show a wider range of immune response than any other group in this Table. Four of 10 of these mice gave a response within the range of the control groups (3, 4 or 7), and thus could be considered non-conditioned (yet all showed comparable taste aversion). In a different model system we have suggested that this failure to condition some mice is an inherent "property" of the mouse and can not be overcome simply by subjecting the animal to further conditioning trials. This model, described below and in Figure 1, assesses skin graft rejection (and its conditioning) in inbred mice.

TABLE I
Classical conditioning of immune suppression using associative learning with cyclophosphamide:saccharin treatment

Pre-treatment[a]	Test[b] trial	Taste[c] preference	IgG-AFC per spleen[d] (range)	
H_2O:PBS	H_2O SACC	0.690.26	35600	(25600-49510)
			31360	(23940-40950)
H_2O:Cy	H_2O SACC	0.710.33	16270	(12110-22030)
			14120	(10600-18960)
SACC:PBS	H2O SACC	0.590.30	33390	(27650-40540)
			36270	(26910-49020)
SACC:Cy	H_2O SACC	-0.360.19	15960	(9870-25850)
			5870	(2230-15520)

Footnotes:

a. Groups of 20 CBA mice on a restricted daily drinking schedule (½ hr per day) were given three I/P/ treatments (21-day intervals) of 100mg/kg cyclophosphamide (Cy) with/without 1% saccharin-flavoured drinking water (Sacc).

b. 21 days after the last trial mice were injected with $5x10^8$ SRBC i.p. and subdivided into groups subsequently given either Sacc or water to drink.

c. Taste preference (for mice offered both water and Sacc in separate bottles) was calculated as in the Materials and Methods.

d. Geometric mean (with range) for IgG-AFC per spleen in groups of mice 7 days after SRBC injection.

Mice given skin grafts from histoincompatible donors reject those grafts at a rate dependent in large degree upon the disparity between donor and recipient at the major histocompatibility complex (MHC). While the destruction of the graft is a complex event, some of the cells whose reactivity can influence the rejection process are now being defined. One such cell, a cytotoxic T lymphocyte,

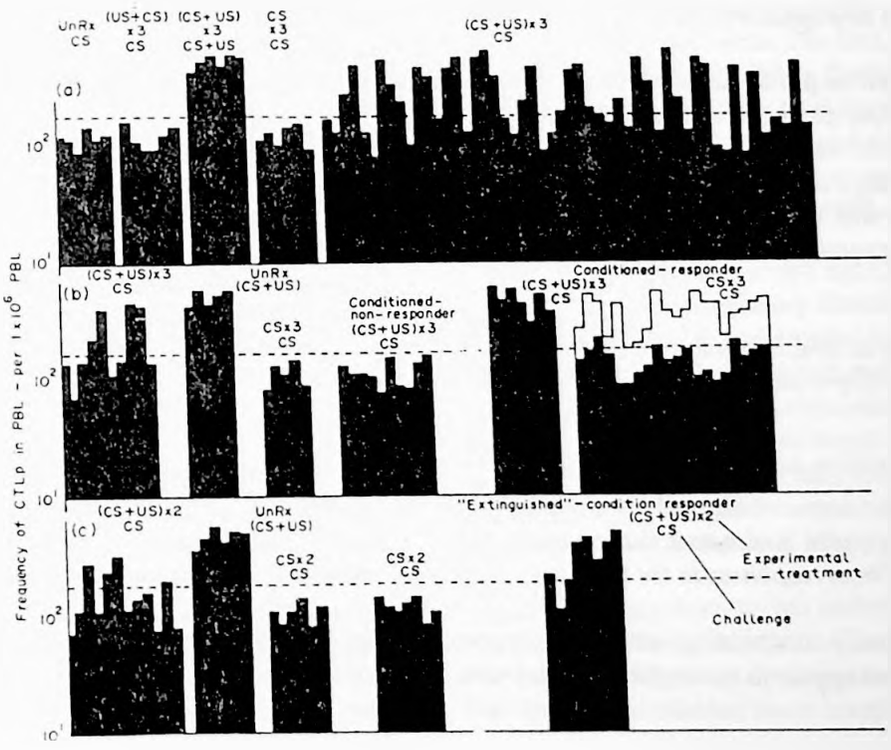
has been reported to play a major role in allograft rejection. This cell, and its precursor (CTLp), can be assayed quantitatively under defined tissue culture conditions. We have shown that at the time when a mouse grafted with foreign skin begins to reject a tissue allograft there is a pronounced (four-fold) increase in frequency of CTLp specific for the graft antigens in the peripheral blood pool. This increased frequency, measured by limiting dilution analysis, subsides to control levels some 40 days after the grafting, but is again apparent when the animals are regrafted. A similar enhanced frequency of allospecific CTLp in the peripheral blood is seen in mice receiving immunization with foreign lymphoid cells i.p. (US). Since the whole procedure of giving an animal a skin allograft necessitates the introduction of a variety of cues (anaesthesia; shaving; wrapping abdomen in protective case etc.), any or all of which may serve as a "conditioning cue", we refer to the skin-graft process as the CS. We have investigated then whether mice given repeated skin grafts (CS + US) will subsequently show elevated frequencies of allospecific CTLp, in the peripheral blood on challenge with a sham graft (CS) alone.

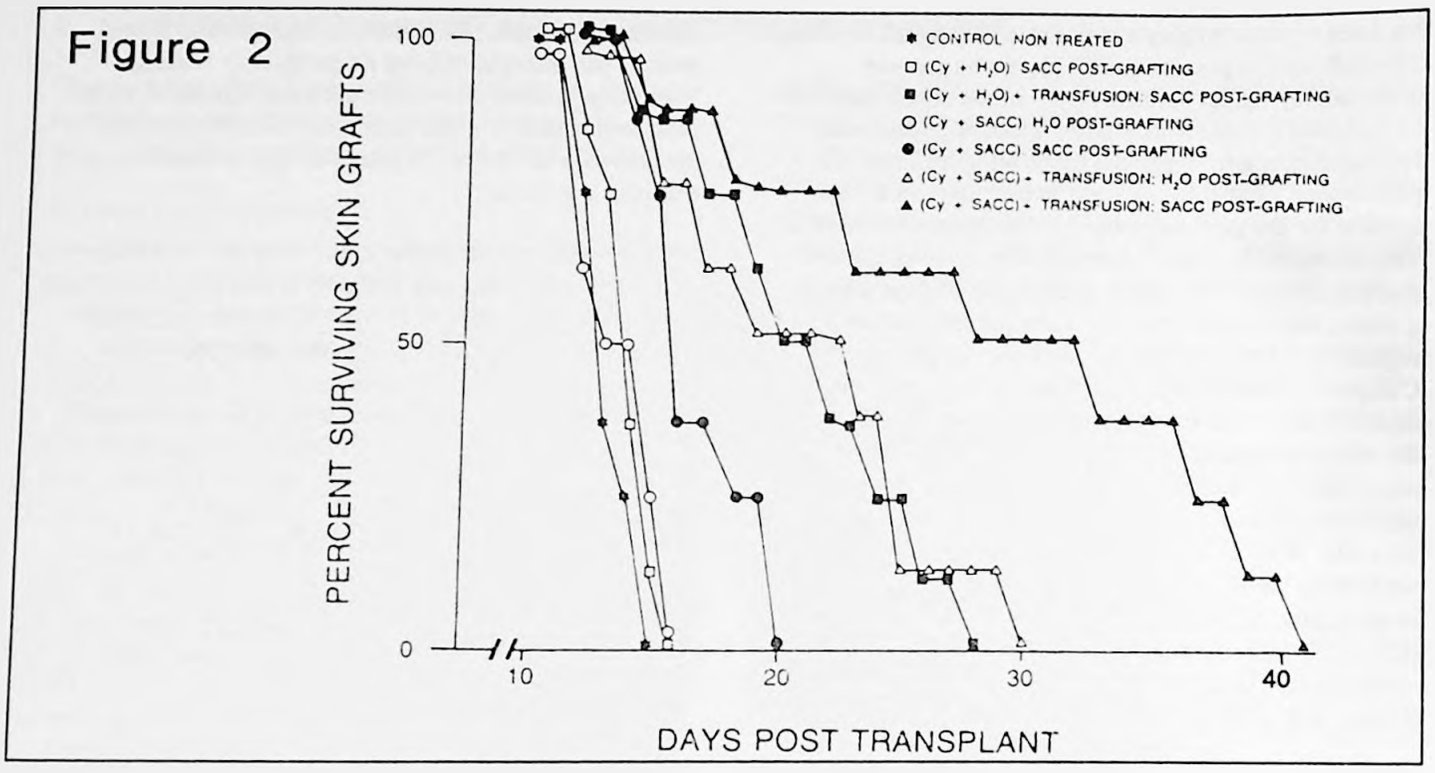
The data of panel a) in Figure 1. show that inbred mice will make a conditioned response after three successive skin grafts. Note that animals given the US and CS in a non-paired fashion (lymphoid cells i.p. followed 7 days later by sham grafting) do not produce this response. The inability to condition all animals of a genetically inbred strain is still unexplained, but a reproducible finding. Interestingly, when non-conditioned mice (panel a) were presented with (CS + US) an additional three times and again re-exposed to the CS (panel b) still no conditioned response was elicited.

Mice showing conditioned enhancement of CTLp frequency in the PBL were randomly assigned to two groups receiving either reinforcement trials (CS + US) or extinction trials (CS alone). As shown in panel b, this latter procedure successfully abolished the response to the CS in previously conditioned mice. In a group selected to be 'conditioned responders', however, when reinforcement is given all mice subsequently continue to make a conditioned response to the CS alone.

Finally (see panel c), despite the fact that phenotypically the extinguished mice seemed to respond now to challenge with the CS like naive individuals, they retained a behavioural memory of their past exposures. Merely two trials with (CS+US) is sufficient to elicit a conditioned response (to CS alone) in such a group of mice (7/8 individuals; mean CTLp frequency 343 + 120 per 10^6 PBL), while this was not as efficient a method when applied to naive mice (panel c: 4/12 "responder", mean CTLp frequency 266 + 53 per 10^6 PBL).

Figure 1





Our most recent work has addressed the question of whether this conditioning of immune reponses has applicability in a clinical situation. We have asked whether conditioned immunosuppression augments skin graft survival in mice in whom graft prolongation is induced by pre-transplant blood transfusion (a standard protocol in e.g., renal transplantation).

Groups of mice were initially pre-treated in a standard protocol known to produce animals displaying conditioned immunosuppression on re-exposure to Sacc.

Control animals received no pre-treatment or (Cy + H_2O) only. Following this, three groups of mice (two CS + US) and one (CS + NCS) were transfused at 7-day intervals with BALB/c blood. Seven days after the last transfusion mice in all groups were grafted with either BAlB/c or C57BL/6 skin grafts as shown and re-exposed to Sacc/H_2O as indicated in the Figure.

Comparison of Mice given BALB/c grafts shows that pre-exposure of mice to (Cy + Sacc) in a conditioning regime produces animals capable of sustaining tissue allografts longer than their control counterparts, if Sacc re-exposure occurred post-grafting (*, □, ○, and ● in Figure 2.)

If animals received no conditioning but were given BALB/c blood prior to grafting, prolongation of grafts was also seen (□, ■).

When conditioned mice were pre-transfused prior to grafting quite different effects were seen on re-exposure to Sacc. If no re-exposure to Sacc occurred, BALB/c graft survival was analogous to non-conditioned mice given transfusion only (■ Δ in Figure). If transfused conditioned mice were re-exposed to Sacc a synergistic enhancement of BALB/c graft survival was seen (compare □, ●, Δ and ▲).

Taken together, these data indicate a profound effect of behaviour on immune functioning, which may have important clinical applications.

Thank You.

During a very brief discussion subsequent to the above presentation the following two points were made.

- *While there have also been conditioned responses for other things such as histamine release, phagocytosis, anaphylactic reactions, etc. the opposite is also true, that is, that the immune system can have an effect on the brain. This is a bidirectional axis. Stress responses in the brain can occur from immune system responses and these also are conditioned.*

- Saccharin is not the only conditioning vehicle. Other smell and taste agents have worked equally well with mice. However, mice do not appear to be conditioned very well by electric bells.

5. THE SIGNIFICANCE OF MOULDS IN INDOOR AIR by DAVID MILLER, PHD

(What follows is an edited summary transcript of Dr. Miller's presentation. Dr. Miller made use of slides.)

There are many measurable indoor pollutants. If the right kinds of expertise are put into investigating every pollutant that can be found in a building they can be identified with certainty and that information can be used. What mostly happens is that a generalist most often examines the indoor air quality in a building when a problem arises. It really takes a great deal of expertise to deal, not only with fungi, but with the many other pollutants. There is no building that just has one contaminant. If a building has a problem it has all kinds of possible pollutants with differing mixtures of them. Compounds that can be isolated from fungi that are known to be harmless by themselves can become very potent when mixed with other toxins or compounds from the same or other fungi.

Another point to make is that, when measurements are made in a building to try to understand what is going on in the space that is affecting people, it is merely a one time snapshot of a complex situation. It is important to realize that dramatic changes can take place over time and from day to day. Thus a measurement can have a remarkable effect on what is perceived.

Of the three kinds of microbials that are of interest, with rare exceptions, fungi are by far the most interesting. Almost all fungi measured outside in an urban environment come from leaves. If comparative measurements were made inside a building or house where the windows are usually kept open in the summer, it is most probable that the findings would be similar as far as fungi are concerned, all other things beings equal. That is the case for the vast majority of buildings and houses in Canada.

In the winter, there are no leaves or fungi in the air. There is snow cover. It is usually quite cold. The windows are closed. The furnace is operating. Whatever the dynamics of the house in terms of fungi or any other pollutant, it is going to be driven by what is going on inside the building.

In the last five years, much has been learned about spores. Fungal spores contain allergens, toxins and other complex chemicals. The first important message is that when moulds are being considered the complexity of the problem has to be kept in mind. There are, at least, 34,000 species of moulds. At least 5,000 of them are common in Canadian buildings. There are many categories of moulds. There are moulds that are pathogens, there are also outdoor moulds like the ones that live on the surfaces of leaves, which do not produce toxins of any importance, but they certainly make allergens. There are fungi from dust in houses that produce very potent toxins. If we were to measure the fungi in this room, we would find that mould is not a unitary property. It is a complex property and different moulds have different biochemistries and thus different potential activities.

The area of most interest now relates to mycotoxins from spores. There are many fungi that make mycotoxins. The most notorious mycotoxins are in food. It has come to be understood in the last five to ten years that if the fungus makes fungal toxins, it puts huge amounts of them in the spores. Inhalation of spores containing huge concentrations will therefore be worth studying. It is known, with absolute certainty, that inhalation of aspergillus flavus spores produces liver cancer.

There is no information on the effects of chronic, low doses of mycotoxins from inhalation exposure. The inhalation by exposure of spores and dusts containing aflatoxin (causing liver cancer) is instructive for a number of reasons besides making the point that the situation occurs. First, the end point - liver cancer - is clear cut and, in western countries, otherwise rare. Secondly, there is a ten-year latency period. Thirdly, aflatoxins are the most potent natural carcinogens. It is very doubtful that there are any other cases of illness caused by inhalation exposure of mycotoxins that could be so readily diagnosed as such. There should be no expectation that inhalation exposure to mycotoxins produces definitive mycotoxicosis. It is more reasonable to assume that the effects will be largely indirect and difficult to detect.

In the last five years there have been a number of epidemiological studies looking at the question of moulds in relation to respiratory illness. The first, a rather small study, was carried out in Britain. While the data are somewhat limited, it suggests that there is an important linkage between the presence of moulds and dampness with respiratory illness. Indoor temperature and humidity were not determinants of respiratory health.

In contrast, the original Harvard Six Cities studies were long term studies of respiratory illness related to outdoor air. A few years ago, it was decided to study indoor air quality and the presence of mould and dampness and the association of a number of serious respiratory symptoms and illness in houses in six northeastern U.S. cities. The results clearly indicated, that next to environmental tobacco smoke, the best predictor for a number of serious respiratory problems was the presence of mould and moisture.

The Canadian government has undertaken a similar study based purely on a questionnaire. The findings are similar to those of the U.S. groups. In the Canadian analysis, it was also determined whether those complaining about

respiratory symptoms, were also allergic. If allergy was the only important cause, one would expect that they would dominate the complaint group. That did not happen. The U.S. investigators found that the correlations with respiratory symptoms did not lie with the sorts of fungi that occur outdoors but with a number of fungi genera that are more commonly indoor fungi and more importantly are known producers of toxins.

The association has been made with mould and dampness. Dampness is a surrogate for many other kinds of building problems. For example, condensation in a house usually means inadequate ventilation rate. Inadequate ventilation rate leads to high concentrations of whatever pollutants are sourced in the house.

Additionally, the role of allergy to house dust mites in relation to symptoms reported has yet to be adequately factored into the analysis. It is clear that such mites are associated with the same kinds of environmental factors that favour mould growth. It is going to take a long time to resolve whether and how much of the symptoms of residents in these houses are driven by fungi alone. The situation is somewhat similar in large buildings except most of them are well maintained and do not have fungal problems, but there are notable exceptions.

In conclusion, it must be affirmed that fungi are very important. The reason why they can impact on our health is not really adequately understood. Probably, the role of many other biochemicals, other than those that induce allergy, is much more important than has been considered. The vast majority of Canadian houses and buildings have airborne mycoflora quantitatively lower and qualitatively identical to outdoor air. For those structures where this is not so, fungi are almost certainly the cause of totally preventable illness. Good building maintenance and awareness of the problem can ensure that the problem disappears. Individuals engaged in research or consulting on this issue need to recognize that the mycological aspects of the problem are not trivial. Further research is needed on sampling approaches, and the effects of inhalation exposure to toxigenic fungi. This research must be interdisciplinary.

Thank You.

During a very brief discussion that followed the preceding presentation, only one question was put to Dr. Miller. The question was, "Are there any documented cases that directly implicate mycotoxins in an actual incident other than the one you cited, namely that of aflatoxins and liver cancer?

Dr. Miller replied, "The simple answer is no. However there have been several cases of extreme exposure to spores in the air. The symptoms that most people associate with such exposure are not symptoms of mycotoxicosis but are in the range that should produce increased susceptibility to disease. The question is difficult to answer because the end point of choice has, as yet, not been determined."

6. MULTIPLE CHEMICAL SENSITIVITIES (MCS): OVERVIEW AND FUTURE DIRECTIONS
by ROBERT McLELLAN, MD

(What follows is an edited version of a written submission of Dr. McLellan's presentation.)

Most clinicians in occupational medicine have seen a growing number of patients who complain of multiple chemical sensitivity (MCS) and note that the clinical presentations are remarkably similar. Indeed, few physicians would dispute that these patients have real problems which are often both chronic and debilitating. Although there are no valid descriptive studies of people with MCS, clinical experience indicates that they are not restricted to a narrow demographic group. They range in age from pre-teens to the elderly and they come from a variety of work settings.

There is, as yet, not sufficient scientific data to state that MCS is a distinct syndrome. Patients who appear to have MCS may have well recognized medical or psychological problems whose unusual presentation may be moulded by cultural phenomena.

Given its clinical prominence and attendant socioeconomic costs, MCS is worthy of serious scientific inquiry. In the end, its etiology is likely to be multifactorial and psychosocial factors will probably be recognized as critical in understanding the natural course of the illness. The physiological abnormalities identified should be major if they are themselves to adequately explain the total debility of many MCS patients.

Before we can design useful research, we must all agree on a case definition - keeping in mind that a case definition for research purposes must often be more restrictive than that used clinically. The notion that MCS is a distinct problem has emerged clinically from the recognition by many practitioners of a similar symptom complex ascribed by patients as related to exposures to environments with low levels of contaminants easily tolerated by most people. Nonetheless, as currently used, the term MCS undoubtedly encompasses several sub-groups. As researchers interested in MCS, we are now in much the same position as those interested in the chronic fatigue syndrome prior to publication of a consensus definition.

Clearly there are many people who have sensitivity to low levels of ambient substances such as those with an isolated sensitivity like TDI asthma; or those with reactive airway dysfunction; or those with "sick building syndrome" (a complex of symptoms which are remarkably like MCS symptoms); or those who develop chemical headaches; or those with cacosmia, a distorted perception of neutral environmental odours that cause distressing symptoms often referable to many organ systems and frequently with prominent neuropsychological symptoms.

At Yale recently, we have developed a research protocol on MCS with a case definition that purposively narrows the group we are talking about. For our project we defined MCS subjects as having;

1. symptoms that involve more than one organ system and must include neuropsychological and respiratory symptoms.

2. symptoms that are distressing and recur predictably in response to environmental stimuli.

3. symptoms that are elicited by a wide variety of common ambient substances and diverse environments that are not troublesome to normal people.

4. a symptom complex that has been acquired and has persisted for at least six months.

5. otherwise generally good health, without any other known medical problems or antecedent psychological problems that could explain their symptoms.

Both my clinical and research approach is to focus on why these patients are so sensitive. The end result of this search may reveal that MCS can best be understood by existing, well characterized diagnoses or perhaps, that it is a discrete entity, requiring new models for understanding human interactions with xenobiotics.

In our search for clues to the etiology of MCS, it is useful to divide chemical exposures into predictable and unpredictable effects.

By predictable effects is meant that knowledge of the toxic and pharmacological properties of the chemical allows a prediction of its health effects based on the dose. There is a well known lower end of the population dose-response curves. This is the intolerant group and environmental policy is often based on trying to protect this sensitive group. The question is, "Does MCS represent this extreme low end of this population dose curve?"

We know that there are many factors that affect a person's place on the population curve. The intolerance might be due to a preexisting disease or constitutional state, or it might be age. Fetuses are more sensitive. Asthmatics are more sensitive. Where people live may affect their tolerance. Those who live in Los Angeles are more tolerant of ozone than those hailing from the Northwest Territories. Genetic

factors such as lactase deficiency lead to intolerance of dairy products.

There are also many factors that, predictably, will affect an individual's tolerance of xenobiotics e.g., chronobiological factors, nutritional state, concomitant chemical exposures, and intercurrent conditions such as viral gastroenteritis resulting in lactose intolerance.

It should also be pointed out that the people at the low end of the population curve may be sensitive to a diverse array of environmental agents. Infants are sensitive to neurotoxins, respiratory irritants, food allergens, radiation, etc. and it is known that people with renal disease may be intolerant to both dietary protein and drugs excreted by the kidney.

What are some of the relevant questions regarding MCS and predictable responses to chemicals?

- Has a historic toxic exposure led to predictable, persistent symptoms that the patient mistakenly identifies as related to incidental daily environmental exposures? There are a number of encephalopathic conditions for example that can be produced by exposure to neurotoxins such as carbon monoxide, mercury, or to solvents.

- Has a historic toxic exposure created an injury which dramatically lowers a person's threshold of tolerance? An injury to mucus membranes of the upper airway might increase sensitivity to irritants. An injury to the lower airways may lead to RADS. RADS may present atypically as a syndrome with prominent neuro-psychological symptoms (associated with hyperventilation precipitated by occult bronchospasm) and chest tightness.

- Have past chronic exposures led to an accumulation of toxins that shift the dose response? It has been suggested without valid confirmation as of yet that people with MCS have an increased xenobiotic burden of a variety of chlorinated hydrocarbons which may modify normal metabolic mechanisms.

- Are there underlying pathophysiological states that shift a patient's dose response curve such as allergic respiratory disease or nutritional deficiencies?

- Does MCS represent an extreme form of the sick building syndrome?

It appears unlikely that the dramatically debilitating aspects of MCS can be fully explained by predictable dose response relationships. The unpredictable effects of chemicals must be considered. By unpredictable effects is meant that the effects cannot be explained by knowledge of the chemical's toxic and pharmacological properties, although some other knowledge of the agents, such as antigenicity, may help.

The classic unpredictable response is allergy. To this classic response, pseudo allergic responses, which present with typical allergic symptoms but appear to have no immunological basis, should be added. TDI asthma is an example.

These typical allergic reactions are quite specific. How can this be related to multiple chemical sensitivities? We cannot really be certain that what people are complaining of as MCS is truly a reaction to multiple different things. It may be to a single agent that is very commonly present but unrecognized. Further, there clearly is a phenomenon of cross reactivity based on similar chemical structures and surprisingly different substances such as synthetic foam and a vegetable may contain similar chemicals. A worker with known TDI asthma developed asthmatic symptoms on eating radishes. Researchers discovered that radishes contain isocyanates.

It is probably going to be important to look beyond classic immunological responses and think about idiosyncratic reactions to chemicals in our environment. There are many examples of this phenomenon to specific chemicals. Unpredictably, halothane causes hepatitis or indocin causes depression in some individuals. Idiosyncratic reactions are usually to specific chemicals but most practising clinicians have had the experience of a few of their patients having a wild and weird response to numerous and diverse drugs.

Can underlying states be identified in MCS patients that might explain their idiosyncratic reactions? Some investigation into possible differences with the nutritional and enzyme systems between MCS and non MCS patients has been undertaken. It has been proposed that there is some difference in essential fatty acid metabolism and in the antioxidant buffering systems that are nutritionally based. Another aspect of interest is the possible association, in at least one sub group, of mitral valve prolapse and autonomic dysregulation. One of my patients with mitral valve prolapse was treated with a beta blocker. Not only were her palpitations helped, but the drug blocked a previous profound "wilting response" to perfumes and other chemicals.

Clinical ecologists have suggested a number of other concepts that are important to consider in trying to understand the unpredictability of chemical response and even, perhaps, the unreliability of response to a particular chemical. One notion is total environmental load. The idea is that it is necessary to know all the concomitant exposures to understand what is going on with someone. There are clear examples where this is important. For example, it is

known that some people can be intolerant of alcohol if they are taking metronidazole.

Another important clinical ecological concept is the issue of the state of adaptation and that this will affect the nature of a person's idiosyncratic response. This hypothesis proposes that a chronic exposure to a substance(s) might produce chronic illness without obvious relation of exposure to symptoms. The theory suggests that removal from the on-going exposure will change the response so that acute effects can be identified on exposure challenge. There are numerous well described examples of this in general medicine such as addiction, response to ozone, humidifier fever or odour detection in general.

Another area of unpredictable response to chemicals requiring investigation involves psychophysiological mechanisms, i.e., behavioural conditioning or "sensitization". Of great interest are the chemosensory effects of low levels of chemicals on the central nervous system. We know odours can affect emotions, behaviour and physiology. There is much research for example on the olfactory limbic link and on pheromones. It is known that women who work or live together tend to synchronize their menstrual periods. It is probable that this has something to do with pheromones. Loring and Schwartz at Yale did some very interesting research where they were able to produce reliable EEG patterns on presentation of specific odourants. These patterns were reliable for an individual but differed for different people for the same odourant.

Shim has published an interesting study in terms of the effect of odours on the pulmonary system and in particular on asthma. Many asthmatics claim that perfume or cologne will provoke their asthma. It is of interest to note that one out of three of Dr. Shim's patients did not develop this response if their noses were clipped, suggesting that a neural link involving the nose was operative.

Finally, a variety of psychiatric explanations need to be considered. One of the most important ones is simply the notion that people who have had an upsetting toxic experience may begin to over interpret and amplify symptoms that they associate with that initial experience. Common examples in general medicine are persons who have had a heart attack and who have associated chest pain with a life threatening event. They are much more likely than a person who has not had a heart attack to panic when they feel a little twinge in their chest.

As we consider the patient presenting with MCS, it is important to think seriously about depression which is a very common and unrecognized disorder frequently associated with an array of somatic complaints. Treatment of depressed people with anti-depressants often helps resolve associated somatic complaints. Somatoform and anxiety and panic disorders clearly have an important role in our consideration.

We must guard against complacency in our evaluation of MCS. Anxiety may become caffeinism when we know how much coffee a person drinks. To get the right answer we must ask the right question. We would be well advised to remember the old adage, "if the only tool available is a hammer, every problem is a nail."

Thank You.

In the discussion following the preceding presentation two questions or comments were raised and responded to by Dr. McLellan.

- *How do you explain what appears to be an apparent contradiction in your presentation? You have stated that continued exposure creates more reactivity and increased sensitivity (in the airways), but you also suggested that continued exposure (to ozone) can lead to a greater tolerance.*

Dr. McLellan replied as follows. "This is a problem that frequently arises when cross sectional studies are attempted in occupational medicine. It is called the Healthy Worker Effect. It is likely that people who fit into this category, for example, people who are troubled by ozone in a particular locale, just leave.

"Clearly there is a group of people who adapt to irritants and probably adapt in a way that is not harmful. There may be a small subgroup of those who adapt to the acute effects but who go on to develop some chronic illness. The main answer to the question is that there is some natural selection here that divides a group into people who actually suffer an injury and then go on to heightened reactivity and those who are able to tolerate and develop increasing tolerance over time.

"Patients sometimes have sensitive psychological antennae with respect to a variety of stressors. These patients who also have MCS are the most unstable and the most difficult to treat. This alludes to the brain immune axis. The point to be made is that MCS should not be ruled out in patients with psychological disorders."

Dr. McLellan went on to add, "People go to doctors mainly because of psychosocial reasons. When we think of the classic MCS patient we are looking at a very skewed population that has a significant amount of psychosocial debility. That debility

is one of the key triggers for getting such a person into the medical system. However, many people in the general population with MCS symptoms may not find them debilitating and thus, may not go for medical help."

7. MULTIPLE CHEMICAL SENSITIVITIES: CASE SELECTION CONSIDERATIONS FOR RESEARCH by LINDA LEE DAVIDOFF, PH.D

Identifying case selection criteria for the condition or conditions known as Multiple Chemical Sensitivities (MCS) is an important but challenging task. At the outset, there is a paradox. It is necessary to define diagnostic criteria for a condition or conditions which are not understood. Although some of us might prefer to postpone the task of defining case selection criteria until the condition has been thoroughly researched and is well understood, the research that is essential for understanding the condition cannot begin until plausible case selection criteria exist for selecting samples for the research. At the same time that science demands case selection criteria, scientists need to be mindful that preliminary criteria are, at best, approximations which will be refined as more is learned.

Given the varied hypotheses and lack of knowledge both about the initial causes of "hypersusceptibility" and about the mechanisms that mediate symptoms after "incitants," case selection criteria for MCS must be descriptive in nature. In defining clinical manifestations of the condition or conditions, one defensible strategy is to select easily identifiable behavioural signs and symptoms.

Table 1: Clinical Criteria of MCS-like Conditions

Low levels of substances evoke responses.
Multiple, unrelated substances evoke responses.
Substances in multiple settings evoke responses.
Symptoms are reproducible with reasonable consistency.
Symptoms resolve after removal from incitants.
An identifiable exposure preceded the onset of the problem.
Symptoms affect more than one body system.
Primary symptoms include neuropsychological symptoms.
The individual exhibits altered sensitivity to odors.
The disorder is chronic.
No single widely accepted test of physiological function correlates with the symptoms.
The individual perceives the response as unpleasant or disturbing.
The individual has sought professional advice.
The individual believes he or she has a disorder.
The individual avoids perceived incitants.

There is reason to believe that the term MCS is being applied at present to a heterogeneous population. MCS or MCS-like conditions have been reported in association with varied exposures to environmental chemicals and as part of the symptom complex accompanying a number of medical conditions, including allergic/inflammatory illnesses (such as hypersensitivity pneumonitis and reactive airway disease), metabolic conditions (such as diabetes mellitus and hypothyroidism or hyperthyroidism), nonallergic upper respiratory conditions (such as rhinitis, nasal polyps, and vocal cord polyps), infections (such as chronic or acute sinusitis and mononucleosis), and the regular use or abuse of medications and recreational drugs. Finally, in numerous cases of MCS or MCS-like conditions with gradual onset, antecedent conditions have been impossible to specify. Eventually, the term MCS may be restricted to a narrow population, but that is not now the case.

Our research has focused on commonalities across what appear to be diverse subpopulations alleging MCS or MCS-like conditions. We have taken two approaches. First, we have tried to enumerate the primary clinical criteria which experts are using. Second, we are attempting to investigate how well the perceptions of affected individuals in different subgroups agree with those of the experts.

In investigating the criteria of experts, primarily medical practitioners, we assembled criteria that had been proposed by groups that had studied MCS-like conditions, including the occupational medicine group at Yale University School of Medicine and the Ontario Ministry of Health Task Force on Environmental Hypersensitivity. We identified the 15 criteria shown in Table 1. We also selected a population of 212 experts utilizing the sources listed in Table 2. We sent them written questionnaires, asking that they specify which criteria they considered "major," "minor," and "irrelevant" for characterizing MCS-like conditions. Two reminder mailings were sent to each invited participant. Of the 212 individuals we approached, 6 could not be reached; 155 responded (some to disqualify themselves because of unfamiliarity with the condition); 126 scoreable questionnaires were returned. Of the scoreable questionnaires, 63% were returned by either allergists (29%), clinical ecologists (16%), or occupational physicians (18%). Of 52 invited allergists, 69% responded; of 40 invited clinical ecologists, 50% responded; and of 31 invited occupational physicians, 74% responded. More than 50% of the 126 responders selected five criteria as "major" for characterizing MCS-like conditions.

Table 2:
Major Sources of Experts for the Study of Major Criteria of MCS-like Conditions

1. Contributors: Workers with Multiple Chemical Sensitivities (1987)
2. NAS Workshop (1987) Participants: On Health Risks from Exposure to Common Indoor Household Products in Allergic or Chronically Diseased Persons
3. NAS Task Force: Subcommittee on Immunotoxicology (1989-1990)
4. Review Board: Maryland Chemical Hypersensitivity Syndrome Study (1989)
5. American College of Physicians: Clinical Efficacy Assessment, Subcommittee and Health and Public Policy Committee (1989)
6. Position Paper Authors: A.I. Terr, E. Kahn, G. Letz (1989)
7. Advisory Panel on Environmental Hypersensitivity Disorders, Toronto (1986)
8. Ad Hoc Committee on Environmental Hypersensitivity Disorders, Toronto (1985)
9. Consults for New Jersey Department of Health Report, Chemical Sensitivity (1989)
10. American Public Health Association MCS Task Force (1989-1990)
11. Editorial Board: Clinical Ecology (1989)
12. Board of Directors: American Academy of Environmental Medicine (1989)
13. Executive Committee: American Academy of Allergy and Immunology (1989)
14. Scientific Board Task Force on Clinical Ecology (California, 1986)
15. Board of Regents of American College of Allergy and Immunology (1989)
16. Board of Directors (physicians only): American Academy of Clinical Toxicology (1989). The similarities which exist between responders who had seen (1) fewer than ten patients and (2) more than ten patients on all but one major criterion (relating to the centrality of multiple organ system symptoms) suggest that judgments about major criteria may have been influenced substantially by something besides personal observations.

(1) reproducible symptoms,

(2) a chronic (persisting) condition,

(3) symptoms following unusually low exposures,

(4) symptoms that resolve or improve when incitants are removed,

(5) symptoms provoked by multiple, unrelated substances.

In a later analysis, we were more selective about our criteria for "expertness" about MCS-like conditions and looked only at the major criteria of responders who had seen 10 or more patients. In this case, 70% of our total sample of 86 responders were either allergists (28%), clinical ecologists (22%), or occupational professionals (20%). For this sample seven criteria were judged "major," the five enumerated above and two others:

(6) symptoms that cannot be predicted by a single diagnostic test,

(7) symptoms that affect more than one bodily system.

Our study of the clinical criteria of MCS-like conditions used by experts had serious flaws in terms of generalizability and of interpretation. Because we could compare only the specialist affiliations of responders and nonresponders, we do not know whether the two groups were comparable in terms of other characteristics and whether our responders were, in fact, representative of the 212 experts we approached. Moreover, we have no way of evaluating the bases of our responders' judgments.

There is a second study in the planning stages to ascertain what affected people say about the signs and symptoms of their condition - to see whether, and to what extent, they report the signs and symptoms which our experts said were characteristic. To collect the impressions of affected individuals, we are in the process of devising a screening survey that translates the criteria endorsed by 50% or more of our experts into behavioural signs and symptoms. We have added additional questions (about odour awareness, types of symptoms, medical status, positive and negative affect, and food intolerance, for example). In some cases, certain of these items discriminated in a pilot study between patients alleging MCS-like conditions and others. We have also included items that will allow us to use statistical controls for certain confounding characteristics (e.g., smoking history, childhood allergies, support group membership). The screening instrument is a telephone interview, which can be converted into a roughly 11-page questionnaire. Our plan is to use the screening survey to characterize several relatively homogeneous samples of people reporting generalized sensitivities to unrelated

chemicals following specific types of exposures: (1) after a nonspecific building-related illness, (2) after pesticide exposures and (3) after exposures to organic solvents in industry. We also want to compare these samples to people alleging overlapping symptoms: atopics and people complaining of sick building syndrome but not of more generalized sensitivities to chemicals. Lastly, we will also screen a sample of the general population to see how common the signs and symptoms of MCS-like conditions appear to be in such a general sample.

We expect studies of varied populations on the screening instrument to yield better descriptive case selection criteria - criteria that reflect both what experts and affected individuals say are characteristic of MCS-like conditions. Such "core" case selection criteria, although preliminary, will be useful for picking samples to answer certain descriptive questions. They might be used, for example, to investigate questions about prevalence, such as how prevalent is MCS or an MCS-like condition among certain atopic populations? among industrial workers? and among office workers?

To adequately study other questions, especially questions about cause and effect, we believe our core criteria will need to be supplemented by additional criteria so that investigators can identify homogeneous study samples. Potentially confounding sources of variation in a study sample include:

1. type of exposure (e.g., organophosphate pesticides, organic solvents, formaldehyde, metals, mixed VOCs, etc.)
2. duration of exposure before the onset of symptoms (e.g., hours vs. years)
3. organ systems of predominant symptoms
4. latency of symptoms after "incitants"
5. time since condition developed (affected individuals report changes in "hypersusceptibility" over time)
6. disability status (people who continue to work will differ from those who do not, along several parameters, including the nature and extent of subsequent exposures)
7. medical history (e.g., atopic status).

Some of these parameters may be considered immaterial for certain types of studies.

Some investigators believe that people with certain medical conditions should not be included in studies of MCS. However, persons can report both asthma, for example, and a MCS-like condition. Since conditions such as asthma or allergy cannot by themselves explain the constellation of signs and symptoms that go along with reports of MCS, individuals with histories of these conditions should not automatically be excluded from research on MCS. Nonetheless, for purposes of certain types of research (e.g., on the causes of symptoms following "incitants"), it seems desirable to select groups who are positive or negative in terms of their history of atopic disorders and other medical conditions. Case selection criteria for specific purposes will also require judicious exclusions. In a chamber study focusing on the causes of symptoms after an "incitant," for example, the following exclusions need to be considered:

1. affected individuals who also have serious illnesses
2. affected individuals who allege serious symptoms after "incitants"
3. affected individuals whose baseline abnormalities will result in uninterpretable findings on chosen endpoints.
4. affected individuals who habitually consume drugs, alcohol, or tobacco
5. unreliable responders under unblinded conditions. (Affected individuals may respond to an "incitant" in an unreliable way for varied reasons - because of sensory cues and attendant psychosocial/psychiatric factors but also because of preceding conditions, such as diet or chemical exposures en route to the experimental setting, or because of hypersusceptibilities to artefactual pollutants within the experimental setting.)

In summary, multiple case selection criteria of MCS are needed at this early stage of understanding. Investigators need a core set of criteria as well as supplementary inclusive and exclusive criteria - depending on the questions of interest.

During a brief discussion pursuant to the preceding presentation, the following two points were made.

- *Factors, such as entitlements to workers' compensation or civil tort actions may influence the symptomatology observed.*

- *There are no known data about dose/response relationships. Thus it is not known whether such links exist and it appears impossible to demonstrate linkage with such conditions as allergies. For example, if we had a population of responders and we did not know who they were, an experiment with that population, using high and low doses would not yield the classic toxicologic - epidemiologic dose response curves. Low doses would give high responses so that the classic dose response patterns would not emerge. It is true that a traditional dose response relationship would provide major evidence.*

REPORTS FROM THE FOUR WORKING GROUPS

1. EPIDEMIOLOGY- Rapporteur: Claire Infante-Rivard, MD

After some discussion, a definition for environmental sensitivity, namely, "idiopathic, polysystem, symptom complex," was chosen. This definition was selected because it is based on description of symptoms and has no built-in etiology. It was also felt that there ought to be a time frame for those symptoms, but there was not enough time to reach an agreement over this issue. From a clinical point of view, it seems that patients who have these symptoms have had them for quite a long period of time.

A good place to start to be able to understand this problem would be to have case series reported. This would be a good way to appreciate what these patients suffer from and provide good descriptions of their symptoms, mode of onset and natural history.

Another suggestion was that general population surveys are needed, either from scratch or by the use of some current data bases, such as, for example, the Ontario Health Survey or Enquête Santé Québec. This would be of assistance in assessing the prevalence of this polysystem complex.

Options to define either a syndrome or a disease from survey data could be either an *a priori* definition based on expert advice, or some form of statistical analysis of the data such as cluster analysis, principal components analysis, or correspondence analysis, etc. This could provide some understanding of how the symptoms are grouped in these patients.

Brief allusion was made to the need for analytical studies with the goal of identifying risk factors. Not enough time was available to discuss how to proceed with such studies. Another meeting would be appropriate for knowledgeable people to try to draw up the kinds of studies that are really needed. One suggestion was made that experts from western Africa could be invited to present data about a possibly relevant condition that has been studied quite extensively there, namely, internal heat fatigue.

Thank You.

During a sometimes intense discussion that resulted from the preceding report, the following questions and comments were made.

- *The opening question actually set the tone for the rest of this discussion. Simply, it was, "How can you do epidemiology if you do not have clear cut diagnostic categories and criteria? For example, do you exclude the chronic fatigue syndrome, Epstein-Barr, etc.?"*

- *In essence the reply consisted of the following: "It is difficult. Yet nothing should be excluded. It seems quite logical to use a terminology for the kind of condition that we are addressing that does not pre decide whether it is environmental or something else. We simply do not know.*

- *"The proposed next steps - case series and analyses of population studies - are equally logical in that the population studies to be examined were or are not conducted for the purpose of looking at environmental sensitivity. These are ordinary surveys where all kinds of symptoms are asked about. From this you can get some kind of framework in which to decide what represents "poly" and how often does it have to be present.*

- *"If you made a list from 100 cases that supposedly represented the condition we are concerned with, every conceivable symptom would be found in the list. We cannot pre decide that only certain symptoms are eligible.*

- *"We have an undefined condition affecting an undefined number of individuals, being treated by an undefined group of professionals which gives us a fair number of variables to deal with. Perhaps it would be better to take what we actually have, namely Dr. Davidoff's definition, something that is concrete, so that we can start with something that is relatively simple. If we do not start with something that is well defined, this could be an exercise in frustration.*

- *"There is place for more than one approach. The working group's suggested method is more in the nature of fact finding. Dr. Davidoff's is one that is more suitable to the situation where one is starting with a clinical population enabling in-depth studies to be carried out.*

- *"The few published case studies are flawed because they suffer from the classic problem of clinicians trying to understand a very biased group of people (eg., from hospital setting, applicants for disability pension etc.). Another series of case studies could just add more smoke unless it was broadly representative and very carefully and scientifically carried out. However, it is necessary to carefully examine the situation to enable the formulation of good questions. Perhaps it would be useful to group those being studied into different populations based, for example on age, occupations, geographic locale, etc.*

- *"It might be possible to define groups of symptoms that appear to occur, more often, in combination than one would predict. If such clusters are found, the next step, namely, analytic studies analyzing for risk factors might be facilitated.*

- *"In a large random survey, the few having serious symptoms can be missed as they might be averaged in with all the normals. A method must be developed to pick up these people. It is true that how the research is designed and carried out is, more often than not, influenced by expectations of certain results, e.g., low incidence versus prevalence of condition."*

The discussion ended with a debate about whether certain symptoms should be excluded. First it was suggested that after the risk factors are examined, certain symptoms could be excluded from the syndrome. This led to the question, "If we assume that the term 'idiopathic' means not knowing the cause of and if a patient has poly symptoms that are not idiopathic, does that mean that this patient gets cut off?" There was certainly a difference of opinion about the answer with no clear cut conclusion.

It was strongly suggested that those with idiopathic and those with non idiopathic symptoms of environmental sensitivity should both be studied. This was countered by the notion that studying those with non idiopathic symptoms, in other words those where the causes of the symptoms are known, would be a waste of time. "We know why they have it. We are worried about those where we do not know why they have it." The universe of illness cannot be examined in one type of study. Its limitations have to be drawn.

2. CHALLENGE STUDIES - Rapporteur: Gordon Sussman, MD

For simplicity, challenge studies were divided into ingestional versus inhalational challenges. With ingestional challenges the consensus was that the symptoms, whatever they are, need to be reproducible in a consistent manner with specific foods or food additives that the patients thought they were sensitive to. Challenges need to be double blind and placebo controlled. It was agreed that a modified restricted elimination diet should be used for one to two weeks, however, because of problems with nutrition and efficiencies the maximum should be four weeks. If patients improved on the diet, they were challenged. The challenge would be done with the food or food additive they found to be most offensive. A maximum of one challenge per week was thought to be the optimum. The time patients should be watched, after the challenge, was generally thought to be within four hours. There was some disagreement because some felt that certain patients could have delayed reactions and thus should be followed longer.

The method of challenge could be with capsules or disguised food. There was some disagreement again. Some thought that larger doses of disguised foods could be given than is possible with capsules. Challenges should be done over two hours with food being given at fifteen-minute intervals. The total dose that could be given was thought to be 10-15 grams with a maximum of 100 grams which is high but felt necessary for some foods. The amount varies depending on the individual food under scrutiny. If a consistent response was not achieved, the challenge should be repeated. The need for an objective end point was emphasized.

As for inhalation challenge, the point was made that there are a large number of anecdotes which should be gathered to assist in providing a date base.

It was recommended that inhalation challenges be carried out in a few specialized centres. An adequate history, in terms of exposure and symptoms is required and a standardized assessment and questionnaire should be used.

Wheezing with changes in pulmonary function, and in others changes in nasal flow rates would provide objective end points. With those having subjective symptoms, it would be necessary to do careful placebo control challenges. This should be done using a standardized and very detailed assessment and the chemicals under scrutiny should be concealed. An attempt to carefully score the symptoms should be made to provide some degree of quantitative assessment.

Again, it was emphasized that there has to be reproducibility of the technique and uniformity in the quality control. All studies should be double blind placebo controlled. The patients should be removed from the

exposure producing symptoms and left until stable. No time limit could be put on it.

The chemicals used in challenge could be a crude mixture (i.e., gasoline fumes) and if abnormalities were found then an analysis of the mixture to identify its components should be undertaken. Some simple components, such as ozone and sulfur dioxide are already known but very little is known about the more complex chemicals.

The recommended dose should be based upon the levels of the patients' exposures to them, especially at work. This should be used as the highest dose in challenges.

Normal controls should be included to gauge the response of symptomatic versus asymptomatic patients and to evaluate the predictability and reliability of the test. The duration of the test was generally thought to be a couple of hours.

Thank You.

During the discussion that followed the preceding report the following questions and comments were raised.

- *"What is the definition of a modified restricted diet? How restricted?" In response it was pointed out there was no total agreement. The point was brought up that there is a modified cave man diet. Generally speaking it consists of a limited number of foods that patients felt that they could tolerate. There was some disagreement in that there are background foods and other foods that patients may be exposed to and not be aware of and that they may be producing symptoms. Foods were limited to 10 or even to 20 that they felt they could tolerate.*

- *It is important in these food challenges to think about the possibility of another layer of complexity and that is the key. Most sensory qualities of the food, whether it be the odour or the taste do, in fact, affect the somatic responses. By disguising taste and smell, important stimuli might be obliterated.*

- *The use of elemental diets and naso gastric tubes for larger amounts was suggested. The problem here, however, is one of patient compliance. Further, utilizing gastric challenge bypasses the mouth and the esophagus and other organs that possibly play a role, such as with chemicals like sulfites. As to elemental diets, patients will not take them for long periods of time.*

- *There was general agreement that reproducibility means that the same symptoms should be reproduced with the same food each time. It is understood that this is not always the case.*

- *There is now a blood test available that measures tryptase, an enzyme that is specific for mast cells. Thus, one can take a sample of blood an hour after the event and if the tryptase level is elevated, it can be assumed that the mast cell has been activated. Tryptase is important because it is much easier to measure than histamine. It is much less labile. It is elevated up to five hours and has a half life of about five hours so that it can be measured after a fairly long period of time. At this time it is still a research tool. Also these reactions may not be mediated by mast cells. The mechanism of these reactions is still not understood so that an end point in the form of a simple blood test is not yet available. The upshot of all this is that the environmental sensitivity syndrome raises a host of questions that urgently need answers.*

- *Synergistic effects were discussed especially in relation to the inhalation challenges and moulds. The difficulty is that one is utilising such non specific symptoms when there is a requirement for reproducible results. Again it was emphasized that an end point is needed, one that can be looked at which in the future may be better than the challenge. Hopefully, as time goes on there will be some other test that will effectively deal with synergism.*

- *A very interesting example of a challenge technique is where an investigator decided to pipe indoor air from a "sick" building to an outside chamber to which passers by were exposed in order to determine whether they developed the symptoms that the people indoors were complaining about. This eliminated the psychosocial parameters. Indeed, it had a positive effect.*

3. LABORATORY APPROACHES - Rapporteur: Deborah Danoff, MD

The discussion started with agreement that this is a problem which requires careful scientific assessment. The "syndrome" requires a definition to be undertaken by the epidemiology group with clinical and basic science input.

The critical question then becomes "Why are these individuals sensitive?" There are two components to the answer. One is the individuals themselves and the other is the environment in which they exist. To arrive at conclusions, a data gathering and analysis process is needed. In terms of clinical research, the first steps are epidemiological definition, and a questionnaire to allow identification of those patients that should be studied. Further analysis would then involve both the individuals and their environments.

Evaluation of the patient would include administration of a questionnaire, physical examination and clinical laboratory testing. There are several questionnaires currently available that could be modified. These include those developed by Health and Welfare and the APCA as well as those used in clinical practice. Physical examination would include general assessment with focus on areas of sensitivity such as the eyes, nasal passages, lungs and autonomic system. Testing that might be included is outlined in Table I. Clinical laboratory testing is outlined in Table II.

Assessment of the environment includes inspection of the home, workplace and possibly the transport system. A questionnaire available from the APCA (Air and Waste Management Association) was suggested as the first step. Evaluation for allergens, toxins, irritants and associated factors is outlined in Table III. Additional suggestions can be obtained from a report of the American Conference of Government Industrial Hygienists. Inspection should be the first step with testing done in a selective manner. Future directions should include a patient registry, data bank and specimen banking system. This would permit controlled analysis of serum and genetic material from individuals as new parameters become identified. In the clinical setting (as opposed to clinical research), at each stage in evaluation, there needs to be a decision tree so that as a precipitant is identified, modification occurs. If the individual improves, no further action is taken. If symptoms recur, additional assessment would be undertaken. The participants also emphasized the need for controlled challenge studies.

To date, the major focus has been on clinical research but attention must also be paid to the possibility of basic science research. At present, the condition is not clearly defined. It is hard to develop an animal model for an undefined condition. Also some of the symptoms which are part of the syndrome are not easily measurable in non-speaking subjects. However, it is clear that the laboratory could be used effectively to look at certain nutritional issues or interaction of nutritional and toxin issues. Here, there is expertise readily available from nutrition and toxicology

TABLE I
CLINICAL EVALUATION OF PATIENTS

Ocular	Schirmer test
	Slit lamp examination
	CO_2 challenge
Nasal	Olfactory acuity
	LIPSET test
	CO_2 challenge
Oral	Saliva production
Respiratory	Pulmonary function tests
	Metacholine challenge
	Hyperventilation test
Cardiac	Assessment for mitral
	valve prolapse
Neurologic	ENG
	Neuropsychiatric testing
	Autonomic system analysis (tilt table, etc.)

TABLE II
LABORATORY EVALUATION OF PATIENTS

Routine	- CBC
	Renal function
	Liver function
	Thyroid function
	Immunoglobulins including IgE
	Chest x-ray
Special	- Carboxyhemoglobin level
	Lead level
	Tryptase level
	Nutritional analysis
	Vitamins
	Trace elements (Mg, etc.)
	Antioxidant enzymes
	Pesticides
	Organic chemicals

TABLE III
ENVIRONMENTAL ASSESSMENT

Allergens - Home	- molds
	- house dust mites
	- animal danders
Work	- appropriate antigens
	Airflow
	Air quality - Indoor Air Quality Kits
	Humidity
	Temperature
	Tracer gas study

groups both in terms of studies which have already gone on and also in terms of suitable animal models.

4. SOCIAL & EDUCATIONAL NEEDS - Rapporteur: Lynn Marshall, MD

The working group had a dynamic discussion. Those organizing this workshop came up with a list of concerns for discussion which the group accepted and added a few more. What follows is the list with the group's comments.

1) Lack of professional awareness and need for professional education

Because of lack of professional awareness, patients' suffering frequently is not acknowledged or assuaged. Information on patient self-help groups, the Allergy Information Association (AIA) and the Allergy and Environmental Health Association (AEHA) are frequently asked of doctors with knowledge of environmental sensitivities. Both organizations have a policy of mentioning no fewer than three physicians. This is difficult because there are so few physicians available with this interest, and standards of training vary in those physicians who are not allergists. There should be minimum educational requirements for those using the term "clinical ecologist."

The AEHA, with the assistance of CSEM, is presently gathering names of physicians who would be sympathetic to patients with environmental sensitivities and could at least offer support. A central registry of such physicians was recommended.

Patients become skeptical of the medical profession when physicians have insufficient knowledge to help them with their health problems. It was of great concern that desperate patients, who cannot find sympathetic or qualified medical assistance, seek out various alternative non-medical practitioners and remedies, some of which could be harmful.

For public credibility, the committee felt that the medical profession has to improve its own awareness. It is up to physicians to pursue continuing medical education, and this is strongly encouraged if hospital privileges are to be retained. However, since there has been disagreement between physician groups, courses pertaining to environmental sensitivities have been denied accreditation, or speakers with knowledge of environmental sensitivities have not been invited to participate in general medical conferences. No information is given to medical students.

Although there is a tremendous amount of activity in the lay press concerning environmental sensitivities, there is very little in the widely read medical, social service and nutritional literature. Articles concerning environmental sensitivity are generally published in highly specialized journals, such as that of the American Academy of Environmental Medicine, which are not read by the bulk of the medical profession. It was hoped that publication of the proceedings of this workshop, and of the results of the Ontario Ministry of Health Studies on Food Allergies will be a start to correcting this discrepancy.

Health and Welfare Canada was commended for drawing together different medical and social service players for this workshop on environmental sensitivities. The Ottawa-Carleton District Health Council sponsored a workshop on the same topic in April, 1990, which had the same effect.

It was suggested that Health and Welfare Canada and the Canadian Public Health Association could cosponsor a national conference on environmental sensitivities, and devise a format for more local awareness-raising seminars.

It was proposed that the provincial ministries of health, provincial hospital associations, and provincial medical associations would sponsor provincial conferences, which would include university educators, as it was thought essential that knowledge of environmental sensitivities get to medical students, and onto CME programs.

The AIA and AEHA could cosponsor workshops at the national, provincial and local branch levels, and draw together the players who are essential from the consumers' point of view.

A concern was expressed that, due to inadequate research knowledge of environmental sensitivities at present, we would be unaware of what awareness to raise. However, the majority felt sufficient knowledge of environmental sensitivities exists to start the educational process. With improved awareness, there may be more research stimulated, and more research funds made available.

The AIA sends out their patient information and newsletters to allergists. It could disseminate them to other groups of doctors.

Since GPs have broad general knowledge, and the most understanding of individual patients and their families, they should be the front-line workers, and the quarterbacks of the health team. With improved awareness of environmental sensitivities and their sequelae, GPs could refer appropriately to various specialists, and then co-ordinate treatment plans. For these reasons, most physicians interested in environmental medicine now only accept patients on referral, as do the allergists.

It would be desirable to have a few specialized teams across the country to act as resources to deal with this condition particularly in its severe form.

2) Need for public education

If there were more public education regarding environmental sensitivities, patients would demand more information from their doctors. However, if the health professionals don't agree, there will not be a health promotion initiative by the federal or provincial governments. The need for raising professional awareness was thus underscored.

Pressure from the public at large, patients' organizations, physicians and MPs has stirred, and will continue to encourage the development of government health policies regarding environmental sensitivities. Pressure at all levels of government would also encourage the development of acceptable public education literature by the Health Promotion Branch of Health and Welfare Canada, the provincial ministries of health, or provincial medical associations.

The committee felt there was a need to focus on health, the "wellness" or "green" model of the whole patient, and the whole environment. The AEHA has an innovative "green teacher movement" whereby teachers improve children's awareness of how to care for the environment and their own bodies. The children then inevitably take some of this knowledge home to their parents.

3) Social stigma attached to the condition

Due to lack of professional and public awareness, there is considerable social stigma experienced by those with environmental sensitivities. When people are suffering, and no one understands their illness, not only do they not get the sympathy and support they need, but they begin to think they are crazy.

Doctors with no knowledge of the illness may dismiss environmentally sensitive patients as "neurotic", implying they are imagining their symptoms, or have some vague, untreatable mental illness. This adds considerably to the suffering of patients and their families.

Even if doctors simply tell patients they can't find anything wrong in the lab tests, patients are likely to assume they must be manufacturing their illness. This deals another heavy blow to self concepts already lowered by a feeling of uselessness resulting from functional loss.

The committee felt the social stigma attached to this disorder also attaches to the physicians who show interest in it. This is hardly conducive to attracting physicians to help these patients. Part of the stigma attached to physicians was thought to be related to the term "clinical ecologist". Originally, the term was coined by Dr. Theron Randolph to signify interest by physicians in the effects of the environment on man's health. Unfortunately, as controversy developed within the medical profession, many non-medical alternative practitioners began to use the term, and confusion ensued as to what clinical ecologists were, or did. It was suggested the term "environmental physician" be used to denote practitioners with an M.D. who have interest and training in environmental medicine.

Inadequate compensation is another reason why it is difficult to attract physicians to environmental medicine. Doctors are paid the same fee for service under provincial Medicare schemes whether they spend a short or a long time assessing patients and doing follow-up visits. Because of multiple system symptoms and multiple environmental illness factors, it almost always takes much longer to do general assessments/consultations, and follow-up visits on patients with environmental sensitivities. This markedly

reduces the number of patients an environmental physician can see in a day, and therefore markedly lowers his/her income.

Patients with environmental sensitivities need unbiased, sympathetic, supportive, guiding physicians, who will look at the whole patient, all his/her needs, and those of his/her family.

Accessibility to treatment is a federal issue, and so the committee thought Health and Welfare Canada could bring pressure to bear on the provincial ministries of health with regard to the need to ensure appropriate care is provided.

The committee thought it would be helpful to identify where there is sympathy and willingness to change, and to focus on this area with educational or policy initiatives. AIA feels British Columbia is the most aware province.

The committee also agreed that ultimately, the costs related to environmental illness will be much higher if patients are not treated.

4) Patients' difficulty coping with some workplace environments, and finding community resources

Again, lack of awareness of varying sensitivity levels in individuals promotes stigmatization in the workplace. Many patients therefore keep quiet, and do not seek medical help if their symptoms are mild. This means the true prevalence of the disorder is completely unknown.

Unfortunately, all the government, and non-government agencies which provide social and housing services or which manufacture products useful to the environmentally sensitive need to know the prevalence in order to do their financial planning. Thus, services are not budgeted, and manufacturers cannot set aside capital for development, production and marketing of suitable products.

The committee thought it was important to find ways to help the patients while studying the epidemiology of the illness concurrently.

If there is inadequate care, lobbying by patients may help the issue to get on to the Ministers' of Health Conference agenda. It was suggested a pilot community be selected, a needs survey done, and then a model developed of how best to meet the needs.

The National Health Research Development Program has money to get different agency or interest groups together to develop protocols for a pilot project.

5) Patients' difficulties obtaining social assistance/pensions

Doctors assessing pension or social assistance applications often have to rely on very sketchy observations of uninformed physicians. The committee felt the definition of disability should be functional, rather than diagnostic. We do not then have to define the disorder before we can decide whether or not a person is disabled. Up until 1984, there was no definition of disability. Now the American Medical Association has guidelines for rating the degree of functional disability. The committee noted that granting of pensions does not solve the problem of the illness, but at least gives suffering individuals and their families some security.

6) Patients' difficulty in meeting illness-related personal expenses, and those related to home environmental changes

There are now some government grants available for home improvements and tax refunds for a few illness-related expenses. There are also some discretionary funds with municipal and provincial family benefits programs to cover some illness-related expenses.

Provincial ministries of health, which license insurance companies, should ensure there is no discrimination against environmentally sensitive patients with regard to payment for medications, serums and assistive devices.

Recommendations

1. There should be minimum educational requirements established for those using the term clinical ecologist. "Environmental physician" would better denote an M.D. with interest and training in environmental medicine.

2. A central registry should be developed of physicians who have appropriate training in this field, and who are sympathetic to the plight of those with environmental sensitivities.

3. These proceedings, and the results of the Ontario Ministry of Health Studies on Food Allergy should be published in widely-read medical journals to raise professional awareness.

4. Health and Welfare Canada and/or the CPHA should sponsor a national conference on environmental sensitivities, and devise a format for more local awareness-raising seminars.

5. Provincial ministries of health, provincial hospital associations, and provincial medical associations should sponsor provincial conferences, and include university educators.

6. Knowledge of environmental sensitivities should be imparted to medical students and to practising physicians through CME programs.

7. The Allergy Information Association, and the Allergy and Environmental Health Association should co-sponsor workshops to draw together the different players who are essential from the environmentally sensitive consumer's point of view.

8. Other groups of doctors besides allergists should receive patient information and newsletters from the Allergy Information Association and the Allergy and Environmental Health Association.

9. GPs should be the frontline workers, referring appropriately to specialists, and then co-ordinating treatment plans.

10. A few specialized teams should be developed across the country to act as resources to deal with environmental illness particularly in its severe form.

11. The public, patients' organizations, physicians and MPs should continue to exhort all levels of government, as this will encourage the development of further government health policies regarding environmental sensitivities, and acceptable public education literature, and, ultimately, a health promotion campaign.

12. Focus should be maintained on the "wellness" or "green" model of the health of the whole patient and the whole environment.

13. Environmentally sensitive patients should not be dismissed as "neurotic", but receive respect and support.

14. Physicians who show interest in the field should not be stigmatized, and should be adequately compensated for the time they spend with patients with complicated illnesses.

15. Health and Welfare Canada should consult with provincial ministries of health to ensure appropriate medical care is provided to environmentally sensitive patients.

16. Education and policy initiatives should initially take place in areas where there is the most sympathy regarding environmental sensitivities, and the most willingness to change.

17. Ways should be found to help patients while epidemiological research proceeds.

18. A pilot study should be done in a selected community, of the prevalence of environmental sensitivities, the needs of patients and models for treatment. Application for grant money to get the various agencies and interest groups together for such a project should be made to N.H.R.D.P. or other agencies with available funds.

19. Disabilities should be rated functionally rather than diagnostically in considering eligibility for pensions/social assistance.

20. Provincial ministries of health, which license insurance companies, should ensure there is no discrimination against environmentally sensitive patients with regard to payment for medications, assistive devices and other illness-related expenses.

Thank You.

Concluding Discussion

The discussion that followed the preceding report concluded the workshop. It consisted of the following questions and comments.

- There are established ways of rating functional disability with normal activities under the neurologic, organic brain or psychiatric syndromes.

- Most physicians have limited insight about occupational and environmental medicine in general, of which MCS is a very small component. The importance of educating primary care physicians about these aspects of medicine has become well recognized. There is an American agency called ATSDR which now funds states to provide this kind of education. Part of this consists of a brief introduction to MCS.

- Groups such as the Thomson Committee certainly have raised the awareness issue. However no one, as yet, appears to be willing or able to really carry the ball to ensure that the recommendations are being carried out. That is the catch.

- The Thomson report just set out a series of recommendations. It presented an opportunity to be pursued. It is hoped that this meeting will have a specific recommendation of "follow up."

- There are two sides to the awareness issue. One of them is awareness of a condition which is multi-system and idiopathic and which contains a lot of symptoms that people have from their daily living. Then there is a shifting into the health care system of a cohort of individuals who really belong within the norms. Patients have often asserted that what they want the physicians to concede is that there is something really wrong with them - a condition and not something in their imagination. This can lead to worry about the possibility of an environmentally-induced neurosis which could fall into a catch basket of poly system disorder. This is one of the problems that physicians face and needs to be resolved. The costs involved in treating everyone with symptoms would be exorbitant.

However, the last thing a patient wants to hear is that he or she is making up his/her symptoms. It has become clear that patients do not make up their symptoms unless there is some particular reason or secondary gain. It is hoped that general practitioners are able to get to know their patients well enough within the family context.

- Up to this point of time there has been no balance in the approach to patients exhibiting these symptoms. There has been in the medical profession, one point of view given continuously, with the other point of view being criticized as being totally unscientific and fraudulent. A balanced approach, including the fact that medicine may not have all the answers, must be based on dialogue. Patients who do not get help from the medical profession will often go to "alternative therapists", who may not have the required training.

- CMHC has a list of all the research it has sponsored on indoor air quality over the last few years. What CMHC has been obliged to do, and it has been useful, is to say, "aren't there some things we can do to housing that will make a difference even though there are a tremendous number of controversies and uncertainties?" A number of studies showed improved health effects when housing improvements were undertaken even though, in most instances the symptoms were multiple and no one could "prove" that any one characteristic of the house was the major cause. The medical community should be made aware that there are some solutions.

- One could adopt a purely pragmatic approach. If a patient is sensitive and one accepts that there is environmental sensitivity then one can take him/her out of the environment as has been suggested. This might be quite expensive but perhaps medical care is even more expensive. As an analogy, it is like saying thirty years ago, someone with renal disease would be put on a kidney machine despite its high cost, since the medical community has nothing better to offer. With research, transplantation becomes less expensive than long term dialysis. It could be argued that what we really need is better research to come up with a medical model that might provide medical treatment as opposed to changing our environment.

- The results of the housing studies were challenged because they did not use a control group. In reply it was simply pointed out that those living in improved housing had their symptoms alleviated. It is true that this does not prove anything.

- The reality is that the environment can make a lot of people sick, especially our housing and work environments. These are much worse than the outdoor environment, the study of which, currently, is the beneficiary of a great deal of money.

- Certainly, there are many reasons to be concerned about indoor air quality that have nothing to do with the probable small percentage of people who have MCS. In fact, a large percentage of people who go into buildings say they feel sick. This has generated a whole industry, both commercial and research, that is desperately looking for ways to improve the quality of indoor air. Many of the technologies that have come out of these efforts have been quite helpful in terms of protecting all of us from such things as carcinogens.

- Pragmatically, a controlled study of housing where a requisite would be the building of different houses would not be very useful. From the literature on placebo-controlled studies it does not appear that any placebo situation can be called inert until everything that is causal is understood. If you improve a house you still cannot know the total chemical background and thus you cannot know exactly what has changed. Thus you cannot say whether there has been a placebo effect until you have identified every single factor involved in this multiple chemical sensitivity and multiple sensitivity response.

- What has happened as a result of CMHC's efforts to improve the houses is to find that building physics, (not medical science), provides some gross causes of why many people get sick and who they are. A significant fraction of houses have a consistent spillage of combustion products and when this occurs the number of people complaining and identifying the sources of their problem is substantial. This is equally true for such things as insulation material. A great deal has been learned because CMHC has gone out to try and solve the problem. It is not science. It is engineering.

The meeting was adjourned after the delegates were thanked for their efforts and the hope expressed that this is the beginning of a host of new, relevant studies.